

intolerance and impaired disposal. After 12 days of treatment with *Panax ginseng* berry extract 150 mg/kg (FIG. 11A), there was a significantly higher rate of glucose disposal at 30, 60 and 120 min ( $P < 0.01$  compared to Day 0). FIG. 11B showed IPGTT data in *db/db* mice after treatment with vehicle, and no significant changes were seen. To evaluate the overall glucose exposure, the area under the concentration curve (AUC) was calculated. A significant improvement in glucose exposure was noted in the 150 mg/kg extract-treated *db/db* mice (Day 12), in which the AUC decreased 53.4% compared to Day 0 (from 814 g/L·min of Day 0 to 379 g/L·min of Day 12,  $P < 0.01$ ). In contrast, there was no significant change in the AUC in *db/db* mice who received vehicle (the AUC was 665 g/L·min of Day 0 and 781 g/L·min of Day 12).

#### ***Panax quinquefolius* berry extract**

Glucose tolerance was evaluated by IPGTT, prior to and 12 days after *Panax quinquefolius* ginseng berry extract treatment. On Day 0, the hyperglycemia in *ob/ob* mice was exacerbated by the IP glucose load, and failed to return to baseline after 120 min, indicating glucose intolerance. Compared to treatment with vehicle (FIG. 12A), after 12 days of treatment with 150 mg/kg berry extract, the overall glucose exposure improved remarkably (FIG. 12B). The area under the curve (AUC) decreased 31.8% after treatment, from 646.6 mg/ml·min of Day 0 to 442.4 mg/ml·min of Day 12 ( $P < 0.01$ ). In vehicle group, however, no significant change was noted in the AUC between Day 0 and Day 12 (from 492.2 mg/ml·min of Day 0 to 497.0 mg/ml·min of Day 12).

#### **Ginsenoside Re**

Ginsenoside Re was also administered at a dose of 150 mg/kg for 12 days to *ob/ob* mice. FIG. 13 shows glucose tolerance evaluated by IPGTT, prior to and 12 days after ginsenoside Re administration. FIG. 13A shows that with a 20 mg/kg ginsenoside Re treatment in lean mice the glucose tolerance was not statistically affected. In comparison, 20 mg/kg ginsenoside Re treatment in *ob/ob* mice (FIG. 13C) significantly decreased the blood glucose levels at 60 min and 120 min following glucose administration (both  $P < 0.01$ ) compared to vehicle-treated *ob/ob* mice (FIG. 13B).

### ***Panax quinquefolius* polysaccharide fraction**

Glucose tolerance was evaluated by IPGTT, prior to and 10 days after treatment with the polysaccharides fraction. As shown in FIG. 14A (150 mg/kg group) and FIG. 4B (50 mg/kg group), on Day 0, *ob/ob* mice demonstrated basal hyperglycemia, and this hyperglycemia was exacerbated by the IP glucose load, and failed to return to baseline after 120 min indicating glucose intolerance. After 10-day treatment with polysaccharides (150 mg/kg and 50 mg/kg), the overall glucose tolerance improved remarkably. After 150 mg/kg and 50 mg/kg polysaccharides treatment, the area under the curve (AUC) decreased 28.2% (from 287.8 mg/ml•min of Day 0 to 206.7 mg/ml•min of Day 10,  $P < 0.01$ ) and 15.5% (from 249.6 mg/ml•min of Day 0 to 211.0 mg/ml•min of Day 10,  $P < 0.05$ ), respectively.

Thus, treatment with ginseng berry extracts, ginsenoside Re or a polysaccharide fractions of ginseng berry improves the ability of the *ob/ob* or *db/db* mice to handle a glucose load or metabolize glucose.

## **EXAMPLE 10**

### **HYPERINSULINEMIC-EUGLYCEMIC CLAMP**

For the glucose clamp study, animals at Day 10 of treatment were catheterized in the right internal jugular vein under general anesthesia. The catheter was externalized through an incision in the skin flap at the vertex of the head. The catheterized animals were allowed to recover for 3-5 days under the continuous treatment of the extract or vehicle before the clamp studies. 120-min hyperinsulinemic-euglycemic clamps (6 mU/kg/min for lean mice, and 10 mU/kg/min for the *ob/ob* mice) were performed on 4 hr fasted mice by maintaining blood glucose concentrations at 6.6 mmol using a variable rate of 20% glucose infusion as previously described (Kim *et al.*, 2000). During the clamps, mice were kept awake in mouse restrainers of proper size. Both glucose and insulin (porcine regular insulin, Eli Lilly, Indianapolis, IN) were administered into the same catheter implanted in the jugular vein through a T-connector. A two-channel microdialysis syringe pump (CMA/ Microdialysis, Acton, MA) was used to control the rate of

infusion. Blood samples were collected from the tail every 10 min during the clamps to measure the glucose levels and adjust the rates of glucose infusion. The average glucose infusion rate in the second half of the clamp was taken as the rate of whole body glucose disposal.

5           Body-wide insulin-stimulated glucose disposal rate with the hyperinsulinemic euglycemic clamp was measured. The rate of glucose disposal by the animals during the insulin stimulation was inferred from the amount of glucose infused per min to maintain blood glucose level at approximately 6.6 mmol. FIG. 15 shows blood glucose levels (FIG. 15A) and exogenous glucose infusion rates (FIG. 15B). Glucose infusion rate for  
10       untreated *ob/ob* mice was only approximately 18% of that in lean controls, indicating a severe peripheral insulin resistance. After a 12-day treatment with 150 mg/kg extract, the rate of insulin-stimulated glucose disposal in *ob/ob* mice was more than doubled relative to the vehicle-treated *ob/ob* mice ( $112 \pm 19.1$  vs.  $52 \pm 11.8$   $\mu\text{mol/kg/min}$  for the vehicle-treated group,  $P < 0.01$ ). Again, the extract did not affect the rate of glucose disposal in  
15       lean control mice ( $400 \pm 53.8$  vs.  $370 \pm 51.4$ ,  $P < 0.01$ ).

Thus, the above data indicate that the ginseng berry extract improved peripheral insulin action. It is contemplated that improved peripheral insulin sensitivity will increase tissue glucose uptake and lower blood glucose levels.

## EXAMPLE 11

### TISSUE-SPECIFIC GLUCOSE UPTAKE

20           After the last blood sample in the hyperinsulinemic euglycemic clamp procedure, mice are sacrificed, and soleus muscle, extensor digitorum longus muscle, interscapular brown adipose tissue, and liver are excised and frozen in liquid nitrogen. The tissues are digested by NaOH and deproteinated as previously described (Wang *et al.*, 1999) or by  
25       the Somogyi procedure. The supernatant from the deproteinated samples is mixed with scintillation cocktail, and  $^{14}\text{C}$  radioactivity will be quantitated (Hom *et al.*, 1984; Ferre *et al.*, 1986). After the plasma samples are deproteinated using the Somogyi procedure, an